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OF THE CHILDREN'S HOSPITAL

WASHINGTON, D. C.

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PANEL SYMPOSIUM: SALICYLATE INTOXICATION*

INTRODUCTION

Joseph M. LoPresti, M.D.†

In 1948, Rubin, et al.,[1] presented a four year survey of 250 children admitted to Children's Hospital following the ingestion of poison. At that time, only 9 of these children were hospitalized because they had ingested salicylate. Kerosene, barbiturates, lye, camphor, turpentine, Chlorox, and cleaning fluids preceded salicylate in the list of ingested poisons. Today, at this institution, salicylate has assumed the number one position in this morbid race. This meteoric rise to unenviable prominence with its attendant cost to the community indicates the pressing nature and importance of this problem. The magnitude of the problem has been compounded by two factors: 1) ignorance by both lay and professional people of the potential hazard of salicylates; and 2) flooding of the market with candy-flavored aspirin tablets. This last factor is the atomic power which has propelled salicylates to their position at the front of ingested poisons.

From the academic viewpoint, the toxicology of salicylate is a fascinating subject. The biochemical changes produced in a child with salicylate intoxication are noteworthy and will be described elsewhere in this issue. At the present time, therapy of salicylate poisoning is a time-consuming, complicated, and expensive proposition. Particularly is this true in the severely intoxicated small infant. We shall present the case histories of 3 patients treated in a new way by exchange transfusion. This treatment, presented as a preliminary report, may be the answer to the problems in management posed by the severely intoxicated small infant.

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* From the meeting of the Combined Pediatric Centers of the Greater Washington Area, presented by the Children's Hospital of Washington, D.C., March 27, 1958.

† Attending Staff, Director, Medical Education, Children's Hospital; Associate Professor, Pediatrics, George Washington University School of Medicine.

CLINICAL ASPECTS OF SALICYLATE INTOXICATION

William R. O'Reilly, M.D.*

Since the introduction of aspirin into clinical medicine in 1899, public acceptance of this household panacea has become so great that annually more than 9 million pounds are consumed by the American public.[1] With that amount at one's disposal, one could treat approximately 6 billion headaches. Any wonder then that we, as physicians, are frequently called upon to treat cases of salicylate intoxication when such widespread usage exists in this country!

In pediatric practice two main situations exist from which salicylate intoxication may result: 1) accidental ingestion of either oil of wintergreen or aspirin, or 2) incorrect dosage of salicylate prescribed by either the parent or the physician in the treatment of disease. Intoxication has been reported following topical salicylate therapy,[2] and rare cases of toxicity associated with hypersensitivity to salicylate have been known to occur.[3,4]

Salicylates, following oral ingestion, can be detected in urine and blood within 30 minutes.[1] Peak blood levels are attained in approximately two hours, after which a slow decline occurs. The drug is rapidly absorbed from the gastrointestinal tract, chiefly the small intestine. After absorption, most of the salicylate is bound to plasma, about 25 per cent, however, being diffused into the interstitial fluid.

Twenty per cent of the absorbed salicylate compounds is destroyed in the body while the majority of the remaining 80 per cent may be found in the urine in the form of free unaltered salicylate, salicyluric acid, gentisic acid and conjugates of glycuronic and salicylic acid.[5]

Although traces of salicylate may be found in the urine a short time after oral ingestion, and despite opinions to the contrary,[6] renal excretion of salicylate is relatively slow; approximately 50 per cent of a given dose is eliminated in 24 hours but trace amounts may be found in the urine up to 48 hours or longer.[1] It is interesting to note that the rate of renal clearance of free salicylate is governed greatly by urine pH. For example, clearance at a pH of less than 7 amounts to only 10 to 15 ml. per minute; at a pH of 7.5, however, clearance may exceed 100 ml. per minute. The work of several investigators[7-11] who attained lower serum salicylate levels by the concomitant administration of sodium bicarbonate with salicylates may be explained by the increased renal clearance in the presence of an alkaline pH. This singular circumstance serves as the basis for one aspect of treatment, for if the urine can be made alkaline, the body will rid itself of free salicylate much more quickly than if the urine is acid.

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The elimination of salicylate in infants is less rapid than in the adult, partly because of immature function of the infant kidney and partly because conjugation, which is an attained function in the body, is not accomplished so well by the infant.[12] In view of this, serious intoxication can occur from cumulative effects of repeated dosage.

The phenomenon of "pyramiding" has been pointed out clearly by Hoffman.[12] If a 60 mg. aspirin tablet is administered every four hours, pyramiding tends to occur, so that at the end of 24 hours the blood salicylate level may be 20–24 mg. per 100 ml. If doses are maintained at this same rate, extreme toxicity will develop in two or three days.

A blood salicylate level of approximately 35 mg. per 100 ml. is generally considered to be the toxic concentration.[12,13] However, because of the wide variability of symptom response by children to levels above and below that magic figure, one point deserves very strong emphasis: "Treat the patient and not the salicylate level." Instances of severe toxicity have occurred at levels far below 35 mg. per 100 ml.[6,14-17] Another item which points out the fallacy of using the salicylate level as the absolute single criterion of whether to treat or not is the fact that signs and symptoms of severe intoxication can persist after the blood salicylate concentration has fallen to well within the therapeutic range.

The major manifestations of intoxication are those resulting from the effect of salicylates on acid-base homeostasis. Biphasic respiratory alkalosis and metabolic acidosis are the hallmarks of the pathologic physiology taking place in the salicylate-intoxicated child. Excellent discussions of the electrolyte imbalance associated with these derangements are available to the interested reader from several sources.[15,18-20]

CLINICAL MANIFESTATIONS

The most common symptoms of salicylate intoxication in children are vomiting and hyperpnea. The vomiting is most likely central in origin rather than an effect of local irritation.[15,21] Hyperpnea is indicative of serious intoxication. Its absence, however, does not mean that the intoxication is mild, for as Winters[18] points out, the hyperpnea of metabolic acidosis is less than that seen in respiratory alkalosis. Furthermore, serious degrees of intoxication can cause exhaustion of the respiratory center and thus an absence of hyperpnea.

Other signs and symptoms of severe intoxication include restlessness, tremor, vertigo, diplopia, maniacal delirium, tetanic or convulsive seizures, hyperthermia, cerebral hemorrhage, acute pulmonary edema and coma. Laboratory-wise, intoxication may be associated with hyperglycemia, and polyuria, proteinuria, and acetonuria.

When one is certain that salicylate ingestion has occured, the diagnosis

is simple. However, a seriously ill, hyperpneic, semicomatose child with hyperglycemia, acetonuria, glycosuria and a lowered carbon dioxide content of the blood could be easily diagnosed as a child with diabetes in acidosis.[22]

After the diagnosis of salicylate intoxication has been made, the question arises whether the patient is presently in a state of metabolic acidosis or of respiratory alkalosis. The use of the carbon dioxide content alone as an indication of one or the other is not justified inasmuch as it is reduced in both. The determination of both serum pH and carbon dioxide content is the only accurate way of estimating which derangement is present.

A factor frequently overlooked in salicylate intoxication is the prothrombin deficiency which many intoxicated children manifest. The bleeding tendencies secondary to the prothrombin deficiency may result in fatal intracranial hemorrhage. Why these patients should develop low prothrombin levels is unknown, except to say that the antiprothrombin substance, Dicumarol®, is chemically very similar to acetylsalicylic acid. It has been proposed that, within the body, salicylate is transformed into Dicumarol or a Dicumarol-like substance. Regardless of the basic biochemical change responsible for this deficiency of prothrombin, the administration of vitamin K combats it and should always be a part of treatment.

PROPHYLAXIS

Perhaps our major concern should be prevention of intoxication. Iatrogenically-induced salicylism as a result of improper dosage schedules suggested by physicians occurs frequently. At the Poison Control Center of this hospital, we routinely give a short lecture to all parents who report that their child has ingested a toxic substance. We point out the hazards of laxity in allowing these products to be available to the searching child. If the tone of our speech is somewhat strong, it is so because we hope to prevent a recurrence of the episode that prompted the initial telephone call.

TREATMENT

The most important considerations in treatment are the correction of acid-base imbalance and the prevention of hemorrhage secondary to hypoprothrombinemia. The judicious use of vitamin K or K_1 oxide in combatting the latter is advocated. Doses of 50 to 75 mg. administered intravenously initially and at three to four hour intervals depending on the prothrombin level are sufficient to prevent bleeding.

The correction of acid-base imbalance cannot properly be instituted until blood or urine pH and carbon dioxide content determinations have been made. Pending these findings, intravenous glucose solutions should be started in amounts to supply full maintenance requirements and to replace the deficits incurred from vomiting and dehydration. When respiratory al-

kalosis is present, isotonic saline administered intravenously allows for renal compensation and serves to prevent salt depletion. This period of respiratory alkalosis may be quite transitory and, in our experience, children admitted to the hospital have usually already entered the phase of metabolic acidosis. In the case of metabolic acidosis, alkalinizing solutions (M/6 sodium lactate or 1.4 per cent sodium bicarbonate) should be given. A simple formula to follow in estimating the initial amount of bicarbonate or lactate to be administered is: (40 minus the patient's carbon dioxide combining power in volumes per cent) times 0.8 times the patient's weight in pounds equals the number of milliliters of M/6 sodium lactate or 1.4 per cent sodium bicarbonate to be given.[13] However, frequent reassessment of blood electrolyte and of the clinical condition of the patient is extremely necessary, for patients with respiratory alkalosis may show a quick transition to metabolic acidosis. On the other hand, this metabolic acidosis may rapidly become metabolic alkalosis from too vigorous administration of lactate or bicarbonate.

Therefore, the only dogmatic statement that one can make regarding this phase of treatment is this: Constant bedside attention along with frequent laboratory studies, followed by necessary adjustments in the solutions being administered are the critical, important main points of therapy.

Of late, reports on the use of exchange transfusions[23,24] in methyl salicylate poisoning and the artificial kidney[25-27] in aspirin intoxication have appeared. Elsewhere in this issue the first published report[28] of the efficacy of exchange transfusion in A.S.A. intoxication is recorded. In the hands of skilled trained teams, these offer a valuable specific method for the treatment of salicylate intoxication.

If, however, such is not available, the treatment measures outlined previously may be used with clinically beneficial results. When carefully directed along physiologic lines and formulated according to the vacillating metabolic imbalance taking place, a favorable outcome is usually assured.

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THE CHEMICAL AND ELECTROLYTIC DISTURBANCE IN SALICYLATE INTOXICATION

Donald W. Delaney, M.D.*

Following oral ingestion, salicylates are readily absorbed from the stomach and upper portion of the small intestine, and after absorption are quickly hydrolyzed to salicylic acid in the plasma. From 50 to 80 per cent of this salicylic acid becomes bound to nondiffusible plasma components, probably plasma protein, while the remainder remains in a free state. As the plasma concentration increases, either through the prolonged administration of small amounts of salicylate or through the short administration of large amounts of salicylate, the amount of free plasma salicylic acid increases. It is probably this free salicylate, diffusing readily into the tissues, which causes the metabolic disturbances of salicylate intoxication.

After absorption, salicylic acid is rapidly distributed throughout all bodily tissues and fluids. However, following intravenous administration even to the point of high plasma levels, salicylate is not found in gastric juice; nevertheless, the gastric distress which is usually thought to be due to local irritant effect is present and is probably secondary to some central effect.

Although demonstrable in the urine within a few minutes following administration, salicylic acid is excreted by the kidney at a relatively slow rate. The plasma salicylate level appears to be reduced by 50 per cent during each succeeding 24 hour period. The rate of excretion is also dependent on the pH of the urine. By the administration of bicarbonate, the pH of the urine is raised and a large increase in the amount of free salicylate in the urine results, with subsequent lowering of the plasma level. On the other hand, administration of ammonium chloride lowers the pH of the urine, decreases the excretion of salicylic acid, and thus results in a higher plasma level over a longer period of time. Experimental studies suggest that salicylic acid is not only filtered and reabsorbed by the kidney, but also excreted by the renal tubules. Tubular reabsorption predominates when the urine is acid, and tubular excretion predominates when the urine is alkaline.

Large amounts of salicylic acid produce a number of disorders of metabolism. The two most important are the disturbance in blood coagulation and the disturbance in plasma electrolyte balance.

Hemorrhagic phenomena are seen during salicylate intoxication. In 1943, Link and his associates demonstrated that high blood levels of salicylate produce a hypoprothrombinemia which was preventable by the administration of vitamin K; the exact mechanism of occurrence is not known. It cannot be demonstrated by the addition of salicylates to plasma *in vitro*.

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Animals on a diet low in vitamin K and humans with cirrhosis of the liver are more susceptible to this hypoprothrombinemic activity. Even though ordinary liver function studies are not usually altered in salicylate intoxication, certain enzymatic processes in the liver are affected by large doses of salicylates. Salicylate seems to exert an antivitamin K effect on liver metabolism, so that prothrombin production is impaired. Large doses of vitamin K overcome this effect and should always be administered prophylactically. Salicylates may also lower the fibrinogen content of plasma; it is suggested that salicylic acid may act on the liver to cause failure of synthesis of fibrinogen.

The most important metabolic disturbance of salicylate intoxication is the change in the acid-base balance and electrolyte structure of the plasma. Two distinct disturbances have been recorded in children: respiratory alkalosis and metabolic acidosis.

Respiratory alkalosis results from the hyperpnea caused by the stimulation of salicylic acid either directly on the respiratory center or through afferent vagal fibers from some peripheral receptor mechanism. Intravenous salicylate in animals causes almost immediate hyperventilation. This can be abolished in cats and rabbits following bilateral cervical vagotomy but is not abolished by atropine or extirpation of the carotid bodies. In decerebrate cats, hyperventilation results only if the corpora quadrigemina remain intact. Salicylic acid may therefore act either centrally or on peripheral receptors, or both.

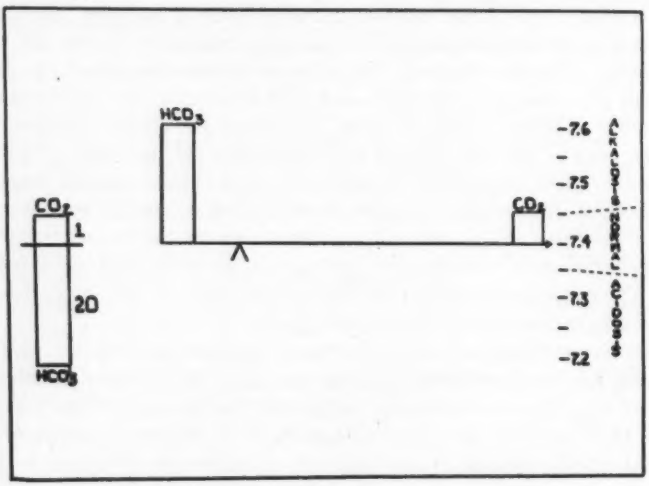

FIG. 1

Whenever the constant blood pH is threatened by metabolic disturbances, the bicarbonate buffer system, wherein the bicarbonate ions and carbonic acid ions are in equilibrium, is called into action. This system is represented by the Henderson-Hasselbalch equation

$$pH = pK^1 + \log \frac{BA}{HA}$$

Under normal conditions when the blood pH equals 7.4 and pK^1 equals the dissociation constant of carbonic acid (6.1), the ratio of the blood bicarbonate (BA) to the blood carbonic acid (HA) is 20 to 1. Depicting this as a balanced scale, figure 1 represents the normal plasma picture with the bicarbonate and carbonic acid (free CO_2) in balance.

With the stimulation of the respiratory center by salicylic acid and the resultant hyperventilation, carbon dioxide is blown off. A lowering of the concentration of the carbonic acid in the plasma results. By referring to the Henderson-Hasselbalch equation, it follows that with reduction of the carbonic acid (HA—the denominator), the value of the blood pH increases; the plasma becomes more alkaline, giving rise to the state of respiratory alkalosis as shown in figure 2. The renal compensation mechanism next comes into play and bicarbonate is excreted by the kidney in the form of sodium bicarbonate in an attempt to bring the pH back toward normal. This results in a compensated decrease in the blood bicarbonate level leading

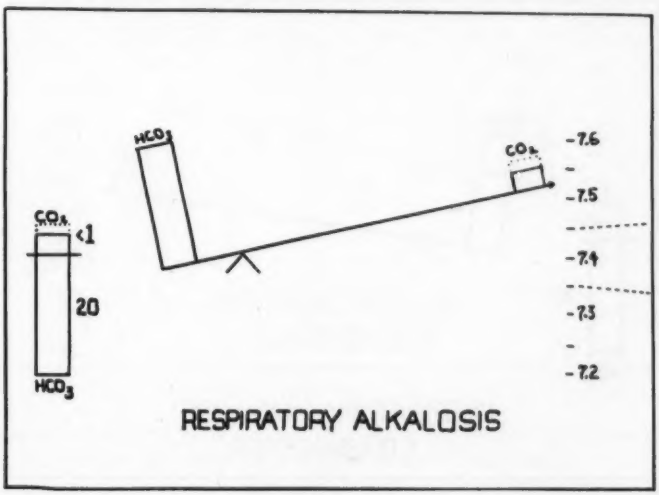

FIG. 2

to a state of compensated respiratory alkalosis (fig. 3). Because of the excretion of sodium bicarbonate, an alkaline urine results. The period of respiratory alkalosis is variable and dependent on the age of the patient. In children it is usually transitory, but it may last for 12 to 24 hours in adults. Metabolic acidosis then follows.

The primary effect in metabolic acidosis is a lowering of the serum bicarbonate due to the accumulation of fixed acids. The cause of the accumulation of these acids is not known. Some authorities believe that it is due to the direct action of salicylate causing failure of adequate glycogen storage in the liver with instead a conversion of glucose to fatty acids. Others more specifically believe that salicylate intoxication involves changes of metabolism at the cellular level with accumulation of organic acid metabolites. Whatever the explanation, these anions which accumulate cause a decrease of the serum bicarbonate with a shift toward the acid side; a state of metabolic acidosis then exists. Figure 4 shows this state of imbalance.

Body compensatory mechanisms again come into action. The shift of blood pH toward the acid side stimulates the respiratory center to blow off carbon dioxide by secondary hyperpnea, thus lowering the carbon dioxide content of the plasma. This mechanism decreases the cation side of the scale and makes the plasma pH less acid; compensated metabolic acidosis then exists, as shown in figure 5. Another renal mechanism also helps to compensate at this point. The kidney manufactures ammonia to combine with

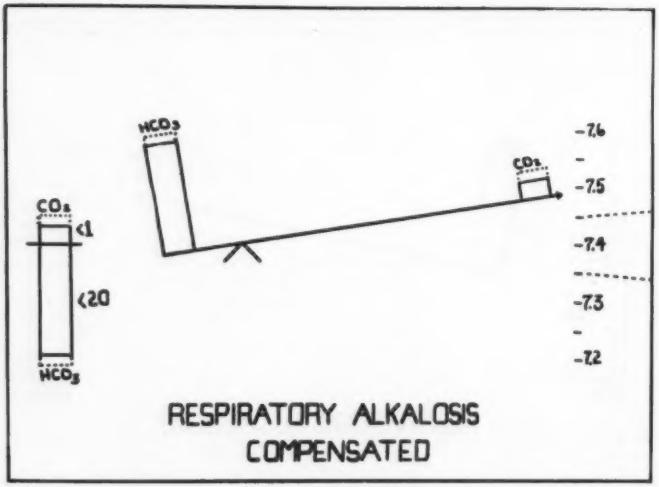

FIG. 3

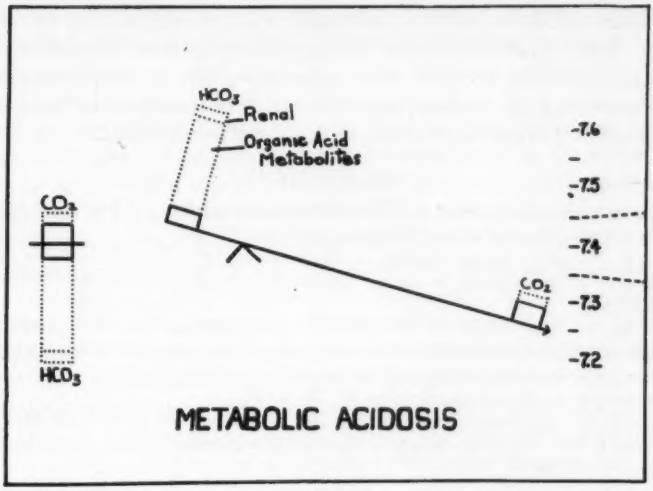

FIG. 4

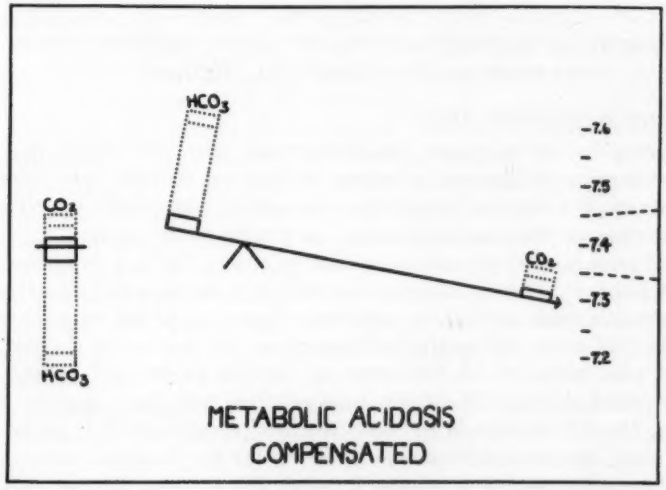

FIG. 5

hydrogen and chloride ions which it excretes in the form of ammonium chloride, thus preserving bicarbonate and forming an acid urine.

Because of the decrease in the amount of ionized calcium occurring during alkalosis, the serum calcium level becomes diminished during the phase of

respiratory alkalosis, and it is necessary to administer calcium to prevent tetany. In the phase of metabolic acidosis, the serum level of ionized calcium becomes increased; however, it is again necessary to administer calcium when correcting this acidosis since restoration of the blood pH toward normal causes a decrease in the amount of ionized serum calcium.

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STATISTICAL REVIEW OF SALICYLATE INTOXICATION AT CHILDREN'S HOSPITAL, 1956–1958

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During the last two years, 132 children have been admitted to this hospital following the ingestion of aspirin in what was thought to be excessive quantities. We have reviewed these 132 charts quite carefully and have made what we think are some rather interesting observations.

The total number of medical admissions during the last two years was 6,554 (table 1). The 132 children admitted with the diagnosis of salicylate intoxication made up slightly more than 2 per cent of the total. In other words, 2 of every 100 medical admissions to this hospital in the last two years were admitted for treatment of "aspirin poisoning." During this same period of time, 476 children were admitted following ingestions of all types. The 132 children in the salicylate group comprised 27.7 per cent of this total, salicylate intoxication being by far the leading cause of hospitalization for ingestions at this hospital. Seventy-one of these children were admitted to the private service and 61 were admitted to the ward service. Sixty-seven of the patients were Negro and 65 were white. Seventy-four were boys and 58 were girls.

A study of the age distribution of these patients (table 2) shows that

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the majority of the cases, 86, or 65 per cent, occurred in children between the ages of 2 and 3½ years, and 106 of these cases, or 80 per cent, occurred in children between the ages of 2 and 4 years. It is interesting that this represents a slightly older age group than is usually seen in other types of ingestions where the majority of cases occur between the ages of 1 and 3 years. One might well postulate that the younger child in the so-called toddler age group may accidentally stumble across the other types of toxic materials and ingest them, while the slightly older child may actually intentionally seek out the aspirin in search of what he thinks is candy.

The seasonal distribution of hospitalization for salicylate intoxication (table 3) was as expected. The peak occurrence was during the winter months, with December, January, and February accounting for by far the largest number of admissions. The six so-called warm months from April through September accounted for 51 cases or 38.7 per cent of the total while the six cooler months from October through March accounted for 81 admissions or 61.3 per cent of the cases. Again, this distribution is not surprising since it is during the cooler months that respiratory illnesses are at a peak and more aspirin is consequently in use. In addition the weather is less favorable, and the children spend more time in the house.

In only nine of the children could a definite history of pica be elicited. An additional five children had a past history of gastric lavage for poison ingestion, and one 3 year old girl had a history of a previous gastric lavage following salicylate ingestion at age 22 months.

Ninety-five of the 132 patients were treated with gastric lavage either in this hospital or in another hospital before being admitted.

The most frequently encountered admitting symptom (table 4) was spontaneous vomiting. Twenty-seven of the children had vomiting as an admitting symptom, 24 had an increased respiratory rate, 8 had some degree of lethargy either by history or as noted on physical examination, and 3 had hallucinations. Two of the children had a petechial rash located on the face and neck, described in both cases as occurring shortly after the aspirin ingestion and disappearing the following day, and one child had a history of tinnitus.

In an attempt to correlate the clinical symptoms with the blood salicylate level, the patients were divided into four groups according to severity of symptoms. Patients who had only one or two episodes of vomiting, with or without a slight increase in respiratory rate (but not exceeding 40 per minute), and those with a slightly increased respiratory rate only, were considered to have mild symptoms. Only those who were actually moribund were considered to be severely affected, and the moderately affected children were considered to be those falling in between the mild and severe groups. Table 5 illustrates that 88, or 66.8 per cent, of all those admitted were

TABLE 1

Admissions 1956–1958

Total Medical Admissions: 6,554	
Salicylate Ingestions: 132 (2%)	
Total Ingestions: 476	
Salicylate Ingestions: 132 (27.7%)	
Distribution of the 132 cases	
Private	71
Ward	61
Negro	67
White	65
Male	74
Female	58

TABLE 2

Age Distribution

Age (in years)	No. of Cases	
0–½	3	
½–1	0	
1–1½	2	
1½–2	8	
2–2½	35	
2½–3	28	106
3–3½	23	(80%)
3½–4	20	
4–5	8	
5–6	5	

TABLE 3

Seasonal Distribution

Month	No. of Cases	
April	13	
May	4	
June	11	51
July	5	38.7%)
August	11	
September	7	
October	14	
November	10	
December	16	81
January	18	(61.3%)
February	15	
March	8	

TABLE 4

Admitting Symptoms

Vomiting	27
Rapid respirations	24
Lethargy	8
Hallucinations	3
Petechial rash	2
Tinnitus	1

completely asymptomatic, while 30, or 22.7 per cent, exhibited only mild symptoms. Ten of the children, or 7.5 per cent, had moderate symptoms, and 4 of the patients, or 3.0 per cent, had severe symptoms. These last 4 were treated with exchange transfusions and responded well. There were no deaths in this series.

The patients were further divided according to the blood salicylate level (table 6). In those 79 patients with blood levels below 45 mg. per 100 ml., 65 had no symptoms, 13 had mild symptoms, and one 5 month old had moderate symptoms. This last case was iatrogenic in origin. Of the 26 children with a blood salicylate level between 45 and 70 mg. per 100 ml., 10 had no symptoms, 13 had mild symptoms, and 3 had moderate symptoms. In the group of 10 children with a salicylate level between 70 and 90 mg. per 100 ml., 1, a 2 year old Negro girl, had a level of 72 mg. per 100 ml. with no symptoms, while 3 had mild symptoms, 5 had moderate symp-

TABLE 5

	Degree of Symptoms			
	none	mild	mod.	severe
Number	88	30	10	4
%	66.8	22.7	7.5	3

TABLE 6

Level of Blood Salicylate (mg. per 100 ml.)	Symptoms			
	none	mild	mod.	sev.
0–45	65	13	1	0
45–70	10	13	3	0
70–90	1 (*72*)*	3	5	1
Over 90	1 (*110*)*	1 (*96*)*	1	3

* Blood Salicylate level expressed in mg. per 100 ml.

TABLE 7

Type of Aspirin

Unknown:	14	
Known:	118	
Candy-flavored children's:	85	(72%)
Nonflavored children's:	12	(10.1%)
Adult:	18	(15.2%)
Both adult and candy-flavored	3	(2.7%)

TABLE 8

Cost of Hospitalization

	Total	Average per patient
Ward	$5,703.60	$93.50
Private	$6,178.95	$87.03
Total	$11,882.55	$90.02

toms, and 1 had severe symptoms. Of the 6 children with a blood salicylate level over 90 mg. per 100 ml., 1, a 2½ year old Negro boy, had a level of 110 mg. per 100 ml. with no symptoms, 1, a 3 year old, had a level of 96 mg. per 100 ml. and exhibited only mild symptoms, while 1 patient had moderate symptoms, and 3 had severe symptoms.

What conclusions can be drawn from the above? It would certainly seem that there is some degree of correlation between the blood salicylate level and the clinical symptoms; however, we have also observed that there appears to be a great variation in the response of two different patients to identical blood levels, as illustrated by the child with a blood salicylate level of 110 mg. per 100 ml. and no symptoms as compared with other children with lower levels and severe symptoms. We have observed, though, that no child over the age of 1 year with a blood salicylate level less than 45 mg. per 100 ml. exhibited more than very mild symptoms.

We also attempted to correlate the clinical findings with the amount of salicylate ingested. In many cases, the exact quantity ingested was unknown and impossible to determine accurately; however, frequently the exact quantity of salicylate ingested was known. We have observed that no child who had ingested a total quantity of salicylate expressed in grains which was less than his body weight in pounds exhibited more than mild symptoms.

Of the 132 cases, 132 were preventable. One hundred twenty-seven

children had themselves found and ingested the aspirin. In 1 case, the grandmother kept feeding aspirin to the child for his fever, not realizing that it was potentially toxic. The remaining 4 cases were iatrogenic in origin, too much being prescribed too frequently for too long a period. Three of these cases occurred in children under the age of 1 year and all were quite ill. It was interesting that 24 children presented almost identical histories. The child had an upper respiratory infection with fever, and the parent or adult in the home had treated it with baby aspirin. Within four hours these 24 children had successfully sought out the bottle of aspirin and emptied it either partially or completely.

It has been suggested that aspirin be packaged in smaller containers. Most baby aspirin sold comes in quantities of either 48 or 50. One might well postulate, in view of information made available to us in this study, that the packaging of aspirin in smaller quantities might play an important role in reducing the incidence of salicylate intoxication.

What are the types of aspirin involved in salicylate intoxication? In 14 of the cases in our series the type of aspirin ingested was unknown; however, in 118 of the cases the exact type was known (table 7). Eighty-five, or 72 per cent, of the 118 cases involved the ingestion of candy-flavored children's aspirin, and an additional 12 cases, or 10.1 per cent, involved nonflavored children's aspirin. Eighteen children, or 15.2 per cent, ingested adult aspirin, while 3 could not make up their mind and swallowed both candy-flavored children's aspirin and adult aspirin.

How much did all this cost the patient and the community? The total cost and average cost per patient is illustrated in table 8. (This does not include the physician's fee in the case of private patients or any expense other than that of hospital treatment.) The total cost of treating the ward patients was $5,703.60, and the average cost per patient was $93.50. The cost of treating the private patients was $6,178.95, and the average cost per patient was $87.03. The total cost of these 132 patients was $11,882.55, and the average for both ward and private patients was $90.02 per patient.

The last and probably least important of our statistics reveals that this $11,882.55 will buy 1,523,660 tablets of the most expensive baby aspirin.

SEVERE SALICYLATE INTOXICATION TREATED BY EXCHANGE TRANSFUSION

Preliminary Report

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INTRODUCTION

The first physicians who tried transfusions in the 17th century began actually by doing replacement transfusions. Eutyphronus remarked that it was foolish to transfuse a patient without previous blood letting. This operation had a few successes and caused quite a few deaths. This is easily understood since the blood employed was of animal origin. In 1664, the Academy of Science in Paris declared that transfusion was a dangerous method, and in 1675, the British Parliament passed a law prohibiting its use.

In 1945,[1] the first attempt was made to use the exchange transfusion for the treatment of hemolytic disease, with subsequent success. In 1949, Bessis[2] reported the use of exchange transfusion in diseases other than hemolytic disease of the newborn. He used it initially in patients with leukemia and was able to produce remissions which were short lived. He reported that there was some improvement in the clinical and hematologic condition of 15 patients and improvement in the bone marrow in 6 patients out of 38 cases studied. He also used this method of treatment in intoxications due to benzol and potassium chlorate, and in hemolytic reaction due to incompatible blood transfusions. In the latter situation he felt that the advantage of this procedure was that it removed the dialyzable and nondialyzable components, and, of course, helped reduce the azotemia which frequently followed these reactions. He also used it in patients with uremia following nephritis and lower nephron nephrosis. Several other workers, including Snapper[3] in this country, have also used the procedure for this purpose. In 1950, Dausset[4] reported 44 cases of lower nephron nephrosis. Four thousand to 7,000 cc. of blood were used, enabling him to improve the azotemia in his patients. Twenty-nine of these 44 patients recovered.

In 1954, Goldbloom[5] treated a 10 year old girl with renal failure and extreme hyperpotassemia with five exchange transfusions. The first pro-

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cedure had a considerable beneficial effect clinically, but succeeding exchanges gradually became less effective and she finally died 42 days after admission. In 1955, Boggs[6] of Philadelphia used this form of therapy for boric acid poisoning. He performed two exsanguination transfusions on a 2.9 Kg., 12 day old infant. In the first he used a liter of blood and in the second 570 cc. He was able to lower the level of boric acid in the blood from 27.5 micrograms to 6.9 micrograms per 100 ml. and the patient recovered. At that time Boggs suggested the use of exchange transfusions in other exogenous poisonings. Since then there have been two single case reports of the use of exchange transfusion in methyl salicylate toxicity,[7, 8] and one of its employment in a case of isoniazid poisoning.[9] All of these patients recovered. Quantities of blood equivalent to one to two times the total blood volume were exchanged, with a drop in the blood level of the toxic substance of 40 to 58 per cent, depending upon the quantity of blood used.

This report summarizes our experience using exchange transfusion in the treatment of 3 children who developed severe salicylate intoxication as a result of ingesting large quantities of aspirin.

CASE 1

This 3 year old Negro boy was admitted to Children's Hospital because of vomiting and progressive difficulty in breathing. Twelve hours prior to the onset of symptoms and 20 hours prior to admission, he had ingested 5 to 10 five grain enteric coated sodium salicylate tablets. On admission he was noted to be an irritable child in acute respiratory distress. The respirations were 60 per minute and heart rate was 140 per minute. Shortly after admission, congestive heart failure developed and rapid digitalization was carried out. Despite conservative therapy directed toward correction of his acid-base imbalance, his respirations became more rapid (80 per minute) and labored, and he gradually became comatose. At this time the child was taken to the operating room where a high left saphenous vein cut-down was done, and a polyethelene catheter inserted. Three hours after admission an exchange transfusion was completed with 2,000 cc. of blood being used (approximately twice the calculated total blood volume).

Halfway through the exchange transfusion, the respirations became improved and the child was more easily aroused. At the end of the transfusion he was fairly alert and his respirations were 44 per minute. Calcium gluconate was given during the procedure in a dose of 2 cc. for each 100 cc. of blood exchanged. He was redigitalized and Mephyton® was given at the end of the exchange. Twenty-four hours after the procedure the salicylate level was 4 mg. per 100 ml., and the child appeared much improved. He was discharged from the hospital, asymptomatic, three days after admission.

CASE 2

This 1 month old male infant had a respiratory illness with fever on February 24, 1958, three days before admission. He was given penicillin intramuscularly, and during the first day of illness was given twelve 1½ grain aspirin tablets. The following day he was no better and received another penicillin injection and sixteen 1½ grain aspirin

tablets. The day before admission he again received sixteen 1½ grain aspirin tablets and the day of admission received one 5 grain aspirin suppository, one 3 grain aspirin suppository and fifteen 1 grain aspirin tablets. During this period the mother felt that the baby did not retain all the aspirin given.

Instead of improving, the temperature became higher and the breathing more difficult; the child became listless and was admitted to the hospital.

On admission, the infant's temperature was 104.6° F. and respirations were 60 per minute and labored. The pulse rate was rapid (180) but regular. There were scattered rales in both lungs. The liver edge was felt 5 cm. below the costal margin. The infant appeared quite listless.

Admission blood count and routine urinalysis were normal. X-ray of the chest showed: "Bilateral emphysema with some infiltration in the upper right chest, most marked at the fifth interspace anteriorly. Bronchiolitis should be considered." Salicylate level was 90 mg. per 100 ml., carbon dioxide combining power 30 volumes per cent, and prothrombin time 65 per cent of normal.

Chloromycetin was given for the respiratory tract infection, the infant was digitalized, and routine treatment for salicylate poisoning consisting of parenteral solutions of sodium bicarbonate and intravenous Mephyton® was instituted. Twelve hours after admission, despite treatment, the blood salicylate level was 103 mg. per 100 ml. and the carbon dioxide combining power was 26 volumes per cent. The child was then unresponsive. At this time it was decided to perform an exchange transfusion. Following a high saphenous cut-down and insertion of a polyethylene tube, the infant was exchanged with 1,250 cc. of whole blood, approximately four times his blood volume. Calcium gluconate and Mephyton® were given at the end of the exchange. Halfway through the exchange, the infant became more alert and relaxed, and then dropped off to sleep. At the end of the procedure he was quite alert and had a respiratory rate of 35 per minute. Approximately eight hours later he had a few convulsive-like seizures; lumbar puncture and blood calcium level done at that time were normal. The infant had a subsequent uneventful course. On the third day after admission the blood salicylate level was 17 mg. per 100 ml. and the carbon dioxide combining power was 56 volumes per cent.

CASE 3

This 1½ year old white boy was admitted to Children's Hospital on March 6, 1958. Ninety adult and 50 baby aspirin tablets were ingested among the patient and two other siblings. This fact was recognized about five hours after ingestion. At that time they were taken to another hospital where gastric lavage was performed. When seen at that hospital, other than having a urine positive for salicylate, the infant did not appear to be in any distress. He was transferred to Children's Hospital and by that time appeared anxious and irritable, and was breathing 50 times per minute. Blood salicylate level on admission was 102 mg. per 100 ml. Serum carbon dioxide combining power was 31 volumes per cent.

Following hospitalization the child became progressively more irritable, and his respirations reached 75 per minute. He was becoming gradually unresponsive. Three and one-half hours after admission the infant was taken to the operating room and following an intravenous cut-down, an exchange transfusion using 2,250 cc. of blood was performed (approximately two times the infant's calculated blood volume). Halfway through the procedure the child became alert, began drinking ginger ale and at one time started to climb off the table. Eight hours after the procedure the blood salicylate level was zero.

COMMENT

The first graph (fig. 1) shows the efficiency of the exchange transfusion in the first patient (case 1), the pre-exchange salicylate value being expressed as 100 per cent. The interesting thing is that the decline in the blood salicylate level was followed by a rise despite the continuation of the exchange transfusion. This could be an artefact but this possibility appears doubtful as it is seen in the second case as well where the same dip and rise occurs (fig. 2). At 1,250 cc., approximately 50 per cent of his salicylate was removed, based on the blood levels. Figure 3 shows a similar but not as striking a situation in the last patient presented.

Table I depicts the blood salicylate levels and the quantities of blood collected from the second patient (case 2) during the exsanguination transfusion together with the calculation for amount of salicylate recovered. The total blood salicylate is based on the blood salicylate and blood volume computed on the basis of 80 cc. per Kg. of body weight. A total of 752 mg. of

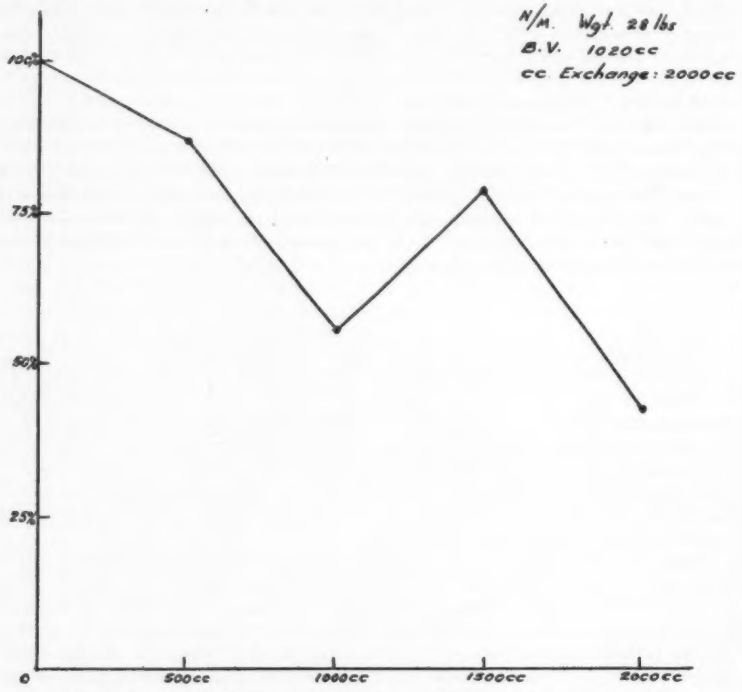

FIG. 1. Efficiency of exchange transfusion on salicylate clearance in case 1, pre-exchange salicylate level being expressed as 100 per cent.

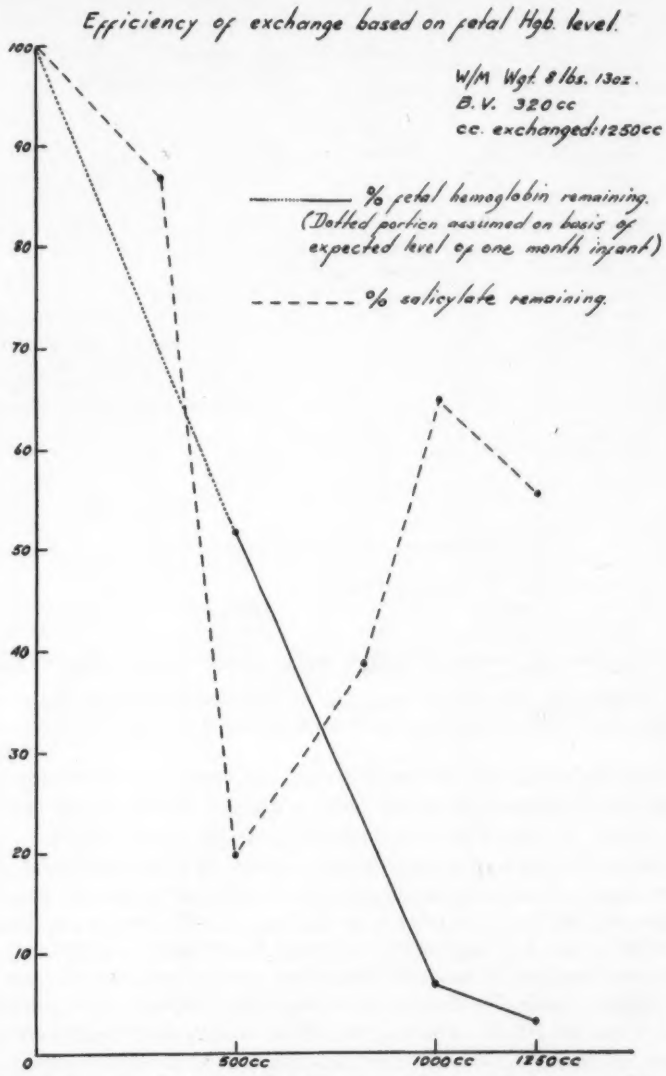

FIG. 2. Comparative removal of salicylate and of red cells (represented by fetal hemoglobin) during exchange transfusion in case 2.

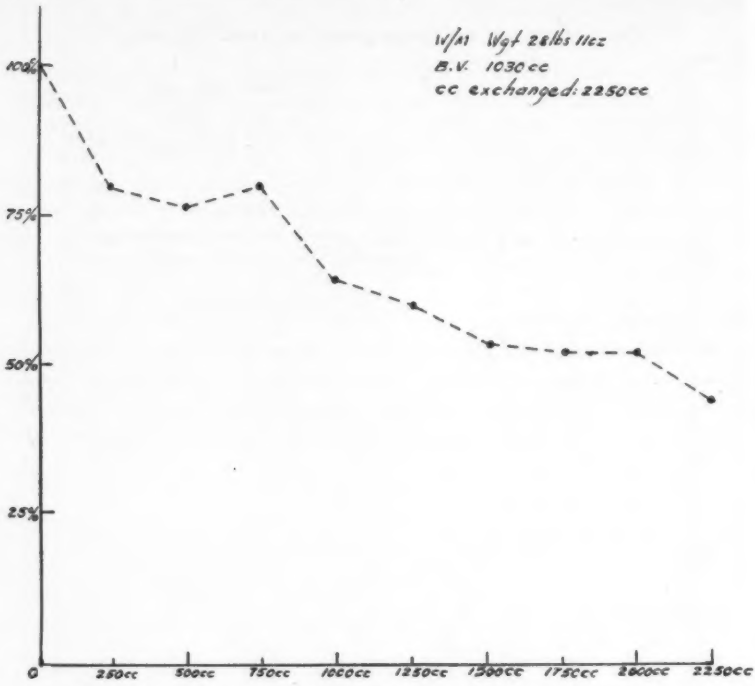

FIG. 3. Efficiency of exchange transfusion on salicylate clearance in case 3, pre-exchange salicylate level being expressed as 100 per cent.

salicylate was recovered. The pre-exchange salicylate level was 92 mg. per 100 ml. and the post-exchange level was 51 mg. per 100 ml. On the basis of these values, 135 mg. was actually cleared from the blood. Therefore, 617 mg. was derived from the extravascular space. This means that in this patient, a 4.5 to 1.0 extravascular to blood salicylate ratio was present. Perhaps this high ratio is related to the fact that this patient had been treated for about four days with very large quantities of salicylate.

The total amount of salicylate recovered in the third patient (case 3) was 1,940 mg. (table II). The change in the patient's blood level of salicylate from 150 mg. per 100 ml. to 69 mg. per 100 ml. is equivalent to a clearance of 835 mg. of salicylate from the blood, leaving 1,105 mg. to be cleared from the extravascular space. This gives an extravascular to vascular ratio of 1.3 to 1.0, a much lower ratio than that found in the previous patient. In patient No. 3 who was treated early, we were able to remove a relatively larger portion of the salicylate from the blood in comparison to the second

TABLE I

Case 2

cc. exchange	mg. % salicylate	Total salicylate recovered
470 cc.	77.8	365 mg.
470 cc.	65.0	310 mg.
150 cc.	51.5	77 mg.
Total salicylate recovered:		752 mg.

	mg. % (Patient)	Total blood salicylate
Pre-exchange	92	295 mg.
Post-exchange	51	160 mg.

Quantity cleared from blood: 135 mg.
Quantity cleared from tissue: 617 mg.

Ratio 4.5:1

TABLE II

Case 3

Total amount salicylate recovered: 1940 mg.

	mg. % salicylate (Patient)	Total blood salicylate level
Pre-exchange	150	1545 mg.
Post-exchange	69	710 mg.

Quantity cleared from blood: 835 mg.
Quantity cleared from tissue: 1105 mg.

Ratio 1.3:1

patient. This, we believe, is probably due to the shorter period of time from ingestion to exchange transfusion in the third patient.

These observations evoke several comments. The removal of a large quantity of salicylate present in the extravascular space by the exchange transfusion may be more important than the lowering of the blood salicylate level in the treatment of the patient. The fact that such a high ratio can occur may be an explanation for the fact that some of these patients may show considerable evidence of toxicity even without a high blood salicylate level. Such toxicity in these children may not be due as much to salicylate sensitivity, as was previously thought, as to a saturation of the tissues. The exchange transfusion may have two different purposes at two different times. Its use early in the course of intoxication may prevent the tissues from becoming saturated while later it may remove the salicylate from the extravascular space.

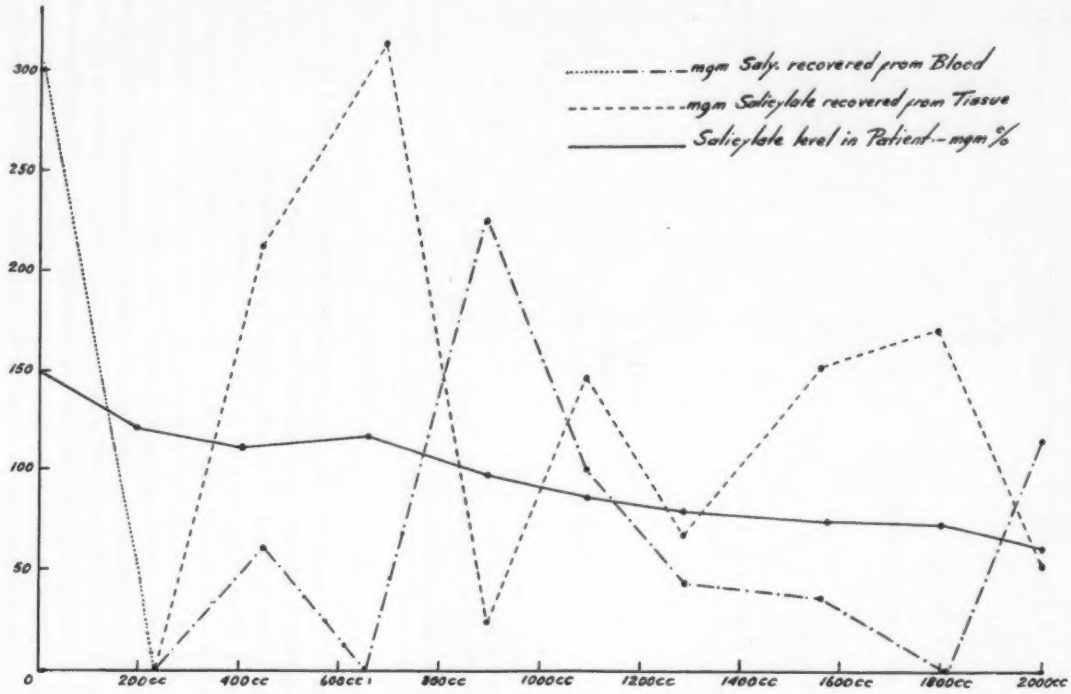

FIG. 4. Change in salicylate concentration occurring in the blood and extravascular space during exchange transfusion in case 3.

Figure 4 demonstrates the changes in salicylate concentration which occurred in the blood and extravascular space during the exchange transfusion in the third patient. By collecting the exchanged blood in 250 ml. portions and performing blood salicylate levels at these same intervals during the exchange transfusion, we were able to estimate which portion of collected salicylate originated in the blood and which portion in extravascular space at these times. These data suggest that a certain quantity of salicylate has to be removed from the blood before any is removed from the extravascular space. Once this point is reached, the amount removed from the blood is small, and the major portion of salicylate removed originates in the tissues. The cycle then repeats itself. This apparent cyclic change may explain the dips and peaks observed in the graphic representation of the salicylate levels in these patients. If concern is based on blood levels alone, a rise in blood level after onset of exchange may cause worry, but it is actually at these points when there is a rise in blood level that a considerable amount is being obtained from the tissues. As may be observed in figure 4, the rises are getting smaller and the amount of salicylate removed decreases with each cycle. The question arises as to when the procedure should be stopped. We stopped when the patients were getting better. Until we have more data, we will have to follow the policy of evaluating primarily the clinical condition of the patient, and secondarily the amount of blood available to us. At this time, it is impossible to say whether two times or four times the blood volume is necessary to exchange the patient adequately.

Exchange transfusion is a very beneficial tool in treating patients with severe salicylate intoxication. The benefits might be summarized as follows: first, the transfusion is readily available in a pediatric center and is an effective method for clearing salicylate from the blood and extravascular space; second, the citrate buffering effect of the blood may be of benefit in correction of acidosis, and the patient is given donor blood which has a higher carbon dioxide combining power; and third, the exchange transfusion can help control any congestive failure which has developed and thereby improve the patient's cardiac status.

SUMMARY

Three children with severe salicylate intoxication were successfully treated by exchange transfusion. Studies on estimated clearance of salicylate from the blood and from the extravascular spaces suggest that 1) the ratio of extravascular to vascular salicylate is related to duration of salicylate ingestion; 2) a certain quantity of salicylate must be removed from the blood before any is removed from the tissues. Thereafter, rises and falls in the blood level are a reflection of salicylate being transported from the

FIG. 4. Change in salicylate concentration occurring in the blood and extravascular space during exchange transfusion in case 3.

tissue pools; and 3) the removal of salicylate from the extravascular space by the exchange transfusion may be more important than the lowering of the blood level *per se*.

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THE EDITOR'S COLUMN

MICROBIOLOGY OF THE MIND

One wonders if the disturbing conflict between the "practical" and the "academic" in the use of antibiotics could be minimized by the resurrection of a partly lost art—microbiological thinking. Simply, this means making full use of the large body of knowledge about clinical and epidemiological features of bacterial infections in the selection of antibiotics for patient care. The clinician using this approach will demand of himself an hypothesis as to the etiology of each infection he diagnoses. As his mind registers "pharyngitis," it will also postulate "probably due to beta hemolytic streptococcus." His hypothesis will require support from the available clinical data on any one patient as compared with the physician's experience and from the physician's knowledge of microbiology and epidemiology. To continue the example: "Beta hemolytic streptococcus—because the youngster has fever and marked erythema of the pharynx and tonsils, a slightly yellow exudate on the tonsils and cervical adenopathy . . . also there has been quite a bit of group A streptococcus around the neighborhood . . . some scarlet fever . . . several positive cultures from other pa-

tients with an indistinct clinical syndrome . . . further, there is little or no evidence to indicate that bacteria other than streptococci cause pharyngitis."

The next steps in the clinician's mind will be concerned with further confirmation of the hypothesis and with selection of treatment. In the example, he may or he may not wish to have a white blood cell count or a throat culture, depending upon how strong his clinical or epidemiological evidence is. To continue the example: "Beta hemolytic streptococcus . . . penicillin is the drug of choice . . . therapy for at least 10 days . . . this child's mother is reliable . . . use an oral preparation . . . been a little worried about the reports that most fatal penicillin reactions follow intramuscular rather than oral administration."

This kind of thinking would force many of us to sharpen our antibiotic-dulled clinical senses. It would probably require some refreshing and updating of our microbiology, epidemiology and "antimicrobiology" from sources other than the "trade" literature.

It would also likely have other results: 1) The microbiology laboratory, when used, would be used to greater advantage. It might even be used less frequently. 2) Antibiotics, when used, would be put to greater advantage with a minimum of danger to the patient. In toto, they would probably be used *much* less frequently. For one example—it is apparently true that little more than 5 per cent of pharyngitis cases are due to bacteria and that virtually all of these are due to streptococci. If this is true, we are not practicing rational therapeutics when we treat a majority of such cases with antibiotics. We are not selecting antibiotics well when we use "wide spectrum" antibiotics rather than penicillin unless there are other reasons. Even if we say that we are using antibiotics *in this case* because we think that streptococci might be present—then we are not consistent if the antibiotic is stopped in two or three days. 3) Infectious disease practice would be much more of a challenge and thereby much more fun. A two minute mental exercise would replace quite a few automatic prescriptions. 4) New information on distinct clinical syndromes and the epidemiology of infectious diseases would accumulate more readily. By looking more closely at this throat and that throat, the clinician can contribute to observational research as correlated with laboratory research. 5) Maybe—the practicing clinician and the microbiologist-academician would shake hands and make up!

R. H. P.

Ed. Note: Readers' comments welcome!

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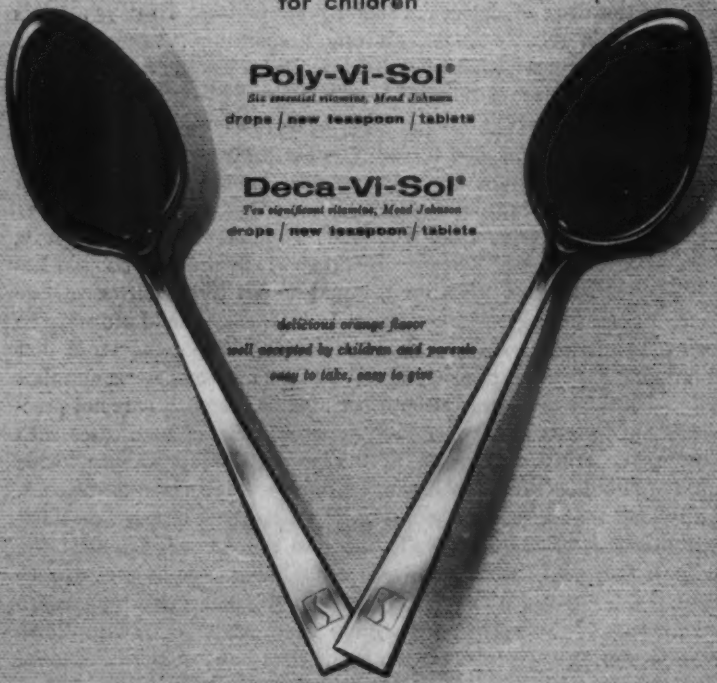

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